CASE: **LA0112 NP**

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney — Type or print name

Signature

September 26, 2006 — Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
TIMUR GUNGOR, ET AL.
APPLICATION NO: **10/775,742**
FILED: **02/10/2004**
FOR: **NOVEL THIAZOLIDINE COMPOUNDS AS CALCIUM SENSING RECEPTOR MODULATORS**

ART UNIT: **1626**
EXAMINER: **STOCKTON, LAURA LYNNE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF YING CHEN

To the Commissioner for Patents and Trademarks:

YING CHEN DECLARES AS FOLLOWS:

1. He has a Master's degree in Organic Chemistry and is a medicinal chemist specializing in the preparation of organic compounds.

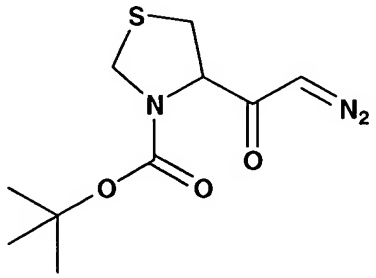
2. He was employed in the above capacity at Bristol-Myers Squibb Company for more than 9 years, and worked under the supervision of Dr. Timur Gungor at Bristol-Myers Squibb Company.

3. He was asked by Dr. Gungor to prepare the compounds which were eventually covered in the subject patent application including Example 1 thereof.

4. That he is not an inventor of the invention claimed in U.S. patent application Serial No. 10/775,742 filed February 10, 2004.

5. That prior to October 22, 2001, experiments were carried out by him under the supervision of Timur Gungor to prepare compounds covered by the claims of the subject application, including the compound of Example 1, which experiments were recorded in Bristol-Myers Squibb Notebook No. 48255 cover page (ATTACHMENT C) and pages 101, 102, 103, 104, 105 and 108, copies of which pages are attached hereto and identified as ATTACHMENTS D, E, F, G, H and I', respectively.

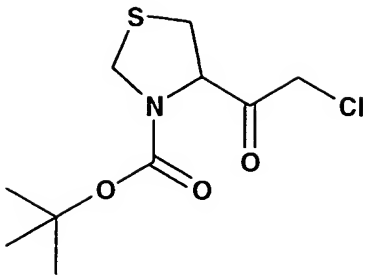
6. On Notebook page 48255-101 (hereinafter page 101) (ATTACHMENT D), entitled Proj. No. 08001, he recorded the preparation of intermediate



from Boc-D-thiazolidine-4-carboxylic acid, which experiment he carried out prior to October 22, 2001.

Page 101 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

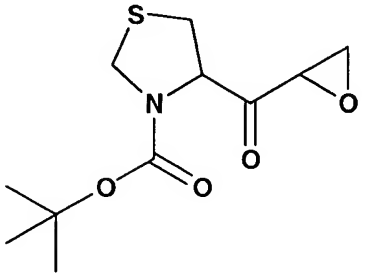
7. On Notebook page 48255-102 (hereinafter page 102) (ATTACHMENT E), entitled Proj. No. 08001, he recorded the preparation of the chloride intermediate



prepared from the intermediate prepared as recorded on page 101 (ATTACHMENT D), which experiment was carried out prior to October 22, 2001.

Page 102 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

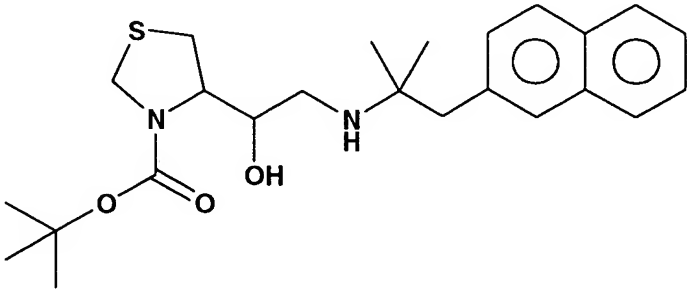
8. On Notebook page 48255-103 (hereinafter page 103) (ATTACHMENT F), entitled Proj. No. 08001, he recorded the preparation of the intermediate



prepared from the chloride intermediate prepared as recorded on page 102 (ATTACHMENT E), which experiment was carried out prior to October 22, 2001.

Page 103 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

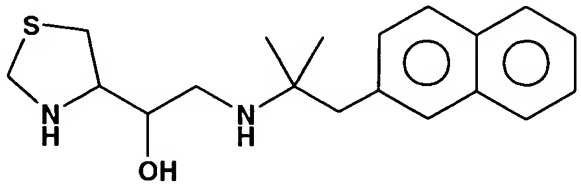
9. On Notebook page 48255-104 (hereinafter page 104) (ATTACHMENT G), entitled Proj. No. 08001, he recorded the preparation of the intermediate



prepared from the intermediate prepared as recorded on page 103 (ATTACHMENT F), which experiment was carried out prior to October 22, 2001.

Page 104 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

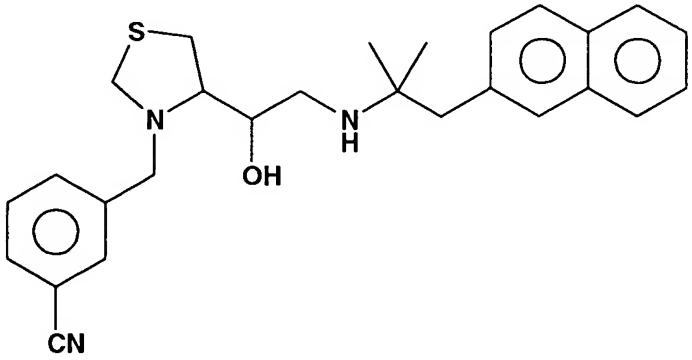
10. On Notebook page 48255-105 (hereinafter page 105) (ATTACHMENT H), entitled Proj. No. 08001, he recorded the preparation of the intermediate



prepared from the intermediate prepared as recorded on page 104 (ATTACHMENT G), which experiment was carried out prior to October 22, 2001.

Page 105 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

11. On Notebook page 48255-108 (hereinafter page 108) (ATTACHMENT I'), entitled Proj. No. 08001, he recorded the preparation of the compound of Example 1 of the subject application



prepared from the intermediate prepared as recorded on page 105 (ATTACHMENT H), which experiment was carried out prior to October 22, 2001.

Page 108 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

12. The actual dates of the experiments regarding the preparation of the Example 1 compound recorded in Notebook No. 48255-101, 102, 103, 104, 105, 108 were carried out and the dates of signing by him and witnessing by Hao Zhang, were all prior to October 22, 2001, but have been obliterated.

13. This Declaration is submitted prior to Final Rejection.

14. The undersigned declares further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 10/775,742 or any patent issued thereon.

Date: 9/26/06

YING CHEN

PROPERTY OF

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

BRISTOL-MYERS SQUIBB

NOTEBOOK No. 48255

Ying Chen
AMGEN

Assigned to Ying Chen

Subject _____

Department Name _____

Department Number _____

Date Assigned _____

Date Completed _____

Pages Completed from _____ to _____

Continued from Notebook Number _____

Continued in Notebook Number _____

This notebook cannot be transferred to another person

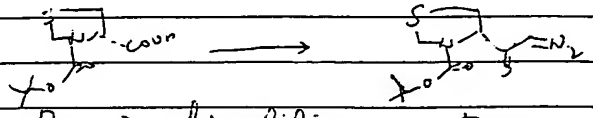
ATTACHMENT C

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

No. 48255-101

DATE: ___ PROJ. NO. 0807 EXPT. NO. ___

SUBJECT ___



Boc-D-thiozolidine	5.0 g	21.4 mmol
-4-carboxylic acid		
Isobutylchloroformate	2.76 ml	21.4 mmol
Et_3N	3.0 ml	21.4 mmol
THF	50 ml	
MNNG	11.7 g	
KOH/H_2O	15 g in 37 ml	
Et_2O	125 ml	

To a two phase solution of KOH and Et_2O at 0°C was added MNNG portionly. The ether layer was decanted to a flask. The fresh made CH_2N_2 in Et_2O was kept at 0°C.
To a solution of Boc-D-thiozolidine-4-carboxylic acid, Et_3N in THF at -10°C (acetone + ice) was added dropwise isobutylchloroformate. The reaction was kept at -10°C for 30 min then filtered (white solid was resulted from $Et_3N \cdot HCl$). The filtrate was stirred at -10°C. A solution of CH_2N_2 in Et_2O was added. Stirring was continued for 1h. Then warmed to RT. $EtOAc$ was added and the solution washed with H_2O, Sat'd $NaHCO_3$ brine and dried over $MgSO_4$. Evaporation gave a yellow oil. Purification was performed by flash column on silica gel, loaded with CH_2Cl_2, eluted with 25% $EtOAc$ in Hexane. Pure fractions were combined and evaporated to give a pale yellow oil.

~~48255-101-24~~ 48255-101-27 4.44 g (80.7%)

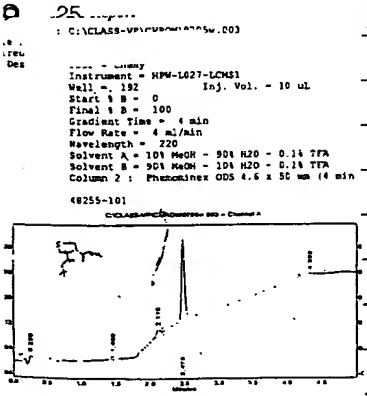
^1HNMR ~~($CDCl_3$, 400 MHz) was consistent~~

$^{13}CNMR$

LC-ms M+23 = 280

RQ22912 for MS M+1 = 258

OK



	RT	Area	Area %	Plates
1	0.26	31325	3.367	161
2	1.43	37489	3.946	2274
3	2.18	55862	6.004	7375
4	2.47	455827	49.001	11173
5	4.33	359915	38.682	0

SIGNED [signature] DATE

WITNESSED AND UNDERSTOOD BY [signature] DATE

CROSS REFERENCES:

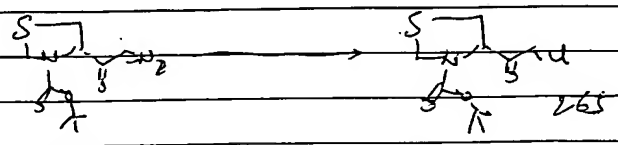
ATTACHMENT D

DO NOT WRITE IN THIS MARGIN

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

DATE: ____ PROJ. NO. 08001 EXPT. NO. ____

SUBJECT ____



5	48255-101-27	44 g
	HCl (4N)	5 ml
	CH_2Cl_2	10 ml

To a solution of 48255-101-27 in CH_2Cl_2 at -10°C, a solution of 4N HCl in dioxan was added dropwise (a lot of bubbles). The reaction was stirred at -10°C for 30 min. HCl was evaporated by a vacuum pump without heating. The rest of solution was warmed to RT. Evaporation was without heat to give a yellow oil. 4.4g

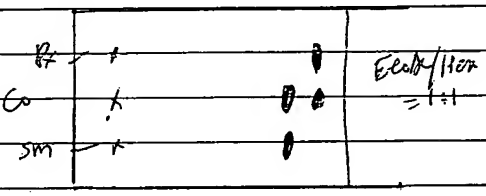
48255-102-1K

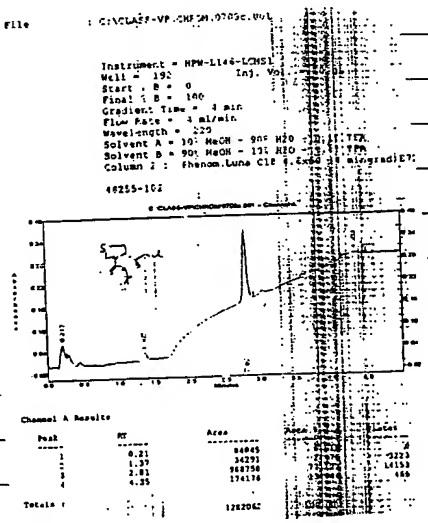
LC-MS M+23 = 288

^{1}HNMR were consistent.

^{13}CNMR

RQ 22935. 7K2703 M-1 = 263.9





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CROSS REFERENCES:

ATTACHMENT E

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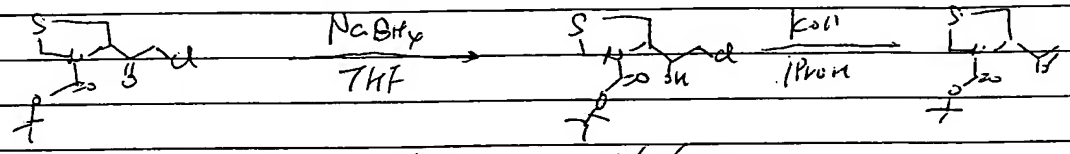
DATE: — PROJ. NO. 08001 EXPT. NO.

SUBJECT



5	48255-102-1X	4.4 g	16.6 mmol
	$NaBH_4$	614 mg	16.6 mmol
	THF	30 ml	

To a solution of 48255-102-1X in THF at RT was added $NaBH_4$. The reaction was stirred at RT for 30 min. LC-ms showed no SM left. HOAc was added to quench the reaction. EtOAc was added and the solution was washed with sat'd $NaHCO_3$, brine and dried over $MgSO_4$. Evaporation gave a crude oil. 48255-103-13

LC-ms showed right M+23 = 2% two isomer ratio 3:1

To a solution of 48255-103-13 in iPrOH (10 ml) was added 4N KOH (10 ml). The mixture was stirred at RT for 1h. EtOAc was added and the organic layer was washed with sat'd $NaHCO_3$, brine and dried over $MgSO_4$. Evaporation gave a crude oil. 48255-103-7B

^{1}HNMR showed two isomer ratio = 2:1

Purification was performed by flash Chromatography on silica gel, loaded with CH2Cl2, eluted with 8% EtOAc in hex. Pure fractions were combined and evaporated to give a colorless oil ~~48~~

Isomer I 48255-103-23 1.2 g

^{1}HNMR and ^{13}CNMR were consistent.

KQ 23050, TR 27387 MS: M+1 = 232.

Isome. II 48255-103-27 1.6 g

KQ 23055

TR 27390 M+1 = 232

SIGNED. DATE - / - WITNESSED AND UNDERSTOOD BY: DATE -

CROSS REFERENCES:

ATTACHMENT F

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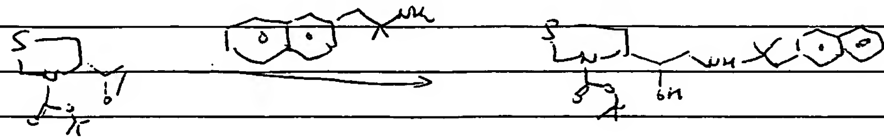
No. 48255-104

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

DATE: PROJ. NO. 08007 EXPT. NO.

SUBJECT



48255-103-23	500 mg	2.17 mmol
amine	432 mg	2.17 mmol

The mixture of 48255-103-23 and amine was heated together at 90 °C for 3 hr. TLC and LC-MS showed no epoxide was left. The reaction was cooled to RT. Purification was performed by flash chromatography on silica gel, loaded with CH_2Cl_2, eluted with 3% MeOH in CH_2Cl_2 + 0.2% NH_4OH. Pure fractions were combined and evaporated to give a colorless oil.

48255-104-14 833 mg (89%)

KQ 23057 BMS-538174-01

ms (TR273554) m+1 = 431

^{1}H NMR, ^{13}C NMR were consistent.

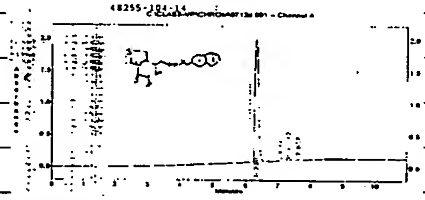
Analytical HPLC Report

File : C:\CLASS-VP\CHROM\0712d.001

7:24:31

Instrument = HPW-L332-HPLC
Well = 177 Inj. Vol. = 10 uL
Start % B = 0
Final % B = 100
Gradient Time = 8 min
Flow Rate = 2.5 ml/min
Wavelength = 220
Solvent A = 10% MeOH - 90% H2O - 0.2% H3PO4
Solvent B = 90% MeOH - 10% H2O - 0.2% H3PO4
Column 1 : Zorbax SB-C18 4.6MM ID X 75MM (8 MIN

48255-104-14



Channel A Results

Peak	RT	Area	Area %	Plates
1	4.33	7622776	96.637	16497
2	7.11	74189	0.965	95392
3	7.21	152876	1.939	96799
4	7.64	31362	0.398	71777
Totals :		7883122	100.000	

SIGNED DATE 1-

WITNESSED AND UNDERSTOOD BY: DATE 1

CROSS REFERENCES:

ATTACHMENT G

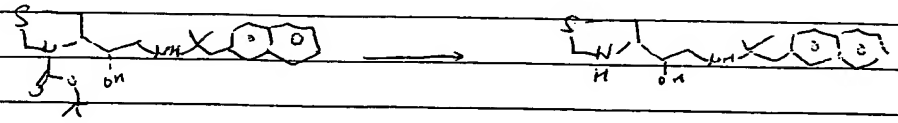
DO NOT WRITE IN THIS MARGIN

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

No. 48255-105

DATE: _____ PROJ. NO. 08007 EXPT. NO. _____

SUBJECT _____

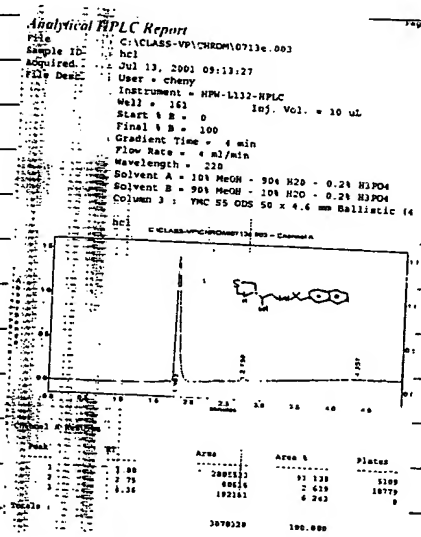


5	48255-104-14	803 mg
	HCl in dioxane	20 ml
	THF	10 ml

To a solution of 48255-104-14 in THF at RT was added 4N HCl in dioxane. The reaction was stirred at RT for 24 hr. Then evaporated to dryness. The residue was dissolved in Sat'd $NaHCO_3$, EtOAc was added and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation gave a pale-yellow oil.

48255-104-14

^1H NMR
^{13}C NMR were consistent. RQ



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SIGNED _____ DATE _____

WITNESSED AND UNDERSTOOD BY: _____

CROSS REFERENCES:

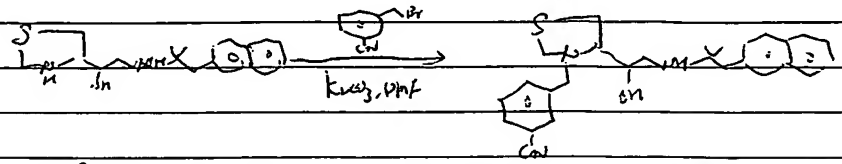
ATTACHMENT H

No. 48255-108

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

DATE: _____ PROJ. NO. 05067 EXPT. NO. _____

SUBJECT _____



5	48255-105-14	100 mg	0.3 mmol
	2-bromotolunitrile	60 mg	0.3 mmol
	K_2CO_3	42 mg	0.3 mmol
	DMF	2 ml	

The mixture of 48255-105-14, 2-bromotolunitrile and K_2CO_3 in DMF was stirred at 40° for 5 hr. then cooled to RT, stirring was continued overweekend. (3 days). EtOAc was added to the the reaction and the solution was washed with H_2O (two times), brine and dried over $MgSO_4$. Purification was performed by flash chromatography on silica gel, loaded with CH_2Cl_2, eluted with 8% CH_3OH in CH_2Cl_2 with 0.2% NH_4OH. Pure fractions were combined and evaporated to give a white foam. HPLC showed small impurities. Purified again by flash column, loaded with CH_2Cl_2, eluted with 1% CH_3OH in EtOAc. Pure fractions were combined and evaporated to give a foam.

48255-105-20

48255-105-20 was dissolved in CH_3OH. HCl in Et_2O (1N / ml) was added. The mixture was stirred at RT for 30 min then evaporated to dryness. 120 mg

48255-105-20

RQ 23496

MS (nominal)

MS (Accurate)

EA

OR

Pka

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CROSS REFERENCES:

ATTACHMENT I